REMARKS

Information Disclosure Statement

An Supplemental Information Disclosure Statement (IDS) was filed on October 1, 2002. Entry of the IDS is respectfully requested.

Objection to The Specification

The Amendment to page 1 of the specification, filed on July 9, 2001, is objected to under 35 U.S.C. § 132 for introducing new matter into the disclosure. The Examiner states that the Amendment has incorporated many new applications by reference. The Examiner indicates that the previous priority claim extended to U.S. Application No. 07/624,114, but not to U.S. Application Nos. 07/492,462 or 07/362,901.

Applicants respectfully point out that the Examiner's characterization of the priority claim of the subject application is incorrect. The application transmittal (copy enclosed) filed with the application on September 1, 2000 contained a specific reference to U.S. Application Nos. 07/492,462 and 07/362,901, claiming priority to these applications and incorporating their contents by reference. Thus, the Amendment of July 9, 2001 merely completes a listing of all priority documents in the related applications paragraph. No new matter was added.

Double Patenting Rejections

U.S. Patent No. 6,379,895 and U.S. Application No. 08/563,759 (Now U.S. Patent No. 6,506,558)

Applicants will consider the filing of a Terminal Disclaimer to overcome the obviousness-type double patenting rejections as appropriate upon notice of otherwise allowable subject matter in the present application. This will permit Applicants to assess the rejections in view of the claims as ultimately indicated to be allowable, since it is possible that the claims may change during the course of prosecution.

U.S. Patent No. 5,143,854

In item 7 of the Office Action, the Examiner states that the double patenting rejection over U.S. Patent No. 5,143,854 is withdrawn. However, in item 11 of the Office Action, the

Examiner states that the double patenting rejection of U.S. Patent No. 5,143,854 is maintained. Clarification is requested.

Rejection of Claims 172-184, 186, and 188-192 Under 35 U.S.C. § 112, First Paragraph (Written Description)

A. Summary of the Rejection

The Examiner states that Claim 172-184, 186, and 188-192 contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. The Examiner states that the specification is directed to the use of photolithographic techniques in methods of making arrays of chemical compounds. However, the Examiner states that the specification does not provide a description for the open-ended method of synthesizing a polypeptide array in the instant claims.

B. Argument

Among other factors, the instant claims are based in part on the inventive concept that polymers can be synthesized by combinatorial methods by the selective application of an activating agent, which will remove protecting groups and subsequently allow growth of a polymer on specific regions of a substrate. Although the methods are largely exemplified by the use of a mask to direct light to specific regions of a substrate, where it removes photosensitive protecting groups, the specification clearly teaches that other activating agents and protecting groups can be employed in a similar manner. At page 63, line 33 through page 64, line 6 of the specification, there is a listing of activating agents other than light, including electron beam irradiation, x-ray irradiation, electric current and electric field (see also U.S. Patent No. 6,379,895). In addition, the specification lists other activating agents such as magnetic fields (see page 19, line 38 through page 20, line 6), chemical agents (e.g., acids, see page 21, lines 7-28), heat (see page 133, lines 26-38), laser pumping (see page 133, lines 26-38), and oxidation and reduction with microelectrodes (see page 133, lines 26-38).

The use of activating agents other than light, along with appropriate protecting groups, for synthesis of a single peptide species on a solid support were well-known in the art at the time of invention. For example, electrolysis was known to remove the protecting group TROC (2,2,2-

trichloroethyloxycarbonyl), which is well-suited for use in oligonucleotide and peptide synthesis (see Semmelhack *et al.*, *J. Am. Chem. Soc.* 94, 5139 (1972) (reference WG) and Van Hijfte and Little, *J. Org. Chem.* 50, 3940 (1985) (reference XG)). The trityl protecting group and the 4-nitrobenzyl-oxycarbonyl protecting group can also be electrochemically removed (see Vairanovsky, *Angew. Chem. Int. Ed. Engl.* 15, 281 (1976)). The t-butoxycarbonyl (t-BOC) is both chemically and thermally labile. Its use and chemical removal are discussed in the present application at page 21, lines 7-28. Geysen (see WO 86/00991) has also reported the use of t-BOC as a chemical protecting group with respect to his methods for the simultaneous synthesis of multiple peptide chain. Also, it was known by 1988 that t-BOC could be thermally removed during the preparation of polypeptides (see Munegumi *et al.*, *Chem. Lett.* 10, 1643 (1988)(reference UG)).

Strategies for the selective removal of protecting groups, such as the protecting groups discussed immediately above, are analogous to those employed for the removal of photosensitive groups. For example, t-BOC can be chemically, thermally, or electrochemically removed by first juxtaposing a substrate with a physical barrier that has holes. In a chemical removal process, the barrier forms a water- or solvent-tight seal with the substrate. Such a barrier is depicted, for example in Figure 11 of U.S. 5,547,839, "Sequence of Surface Immobilized Polymer Utilizing Microfluorescence Detection," by William J. Dower and Stephen P. A. Fodor ("Exhibit B"), which is incorporated by reference on page 1, line 31 of the specification. Subsequent immersion of the substrate in an acid solution selectively activates regions through holes in the barrier. For thermal removal, the barrier blocks certain regions of the substrate from absorbing radiation. Heat can be delivered using, for example, a laser beam by essentially the same strategy as in photodeprotection. For electrodeprotection, a nonconducting barrier can be used in the removal of electrochemical groups. Immersion of the substrate in an electrolyte and applying an electric field deprotects those regions not covered by the barrier.

Other general strategies for the selective removal of protecting groups are disclosed at page 10, lines 6-9 of the specification, where it states that "[d]ifferential reaction is achieved by selectively exposing reactive functional groups to, e.g., light, electric currents, or another spatially localized activator." Examples include electro-optical and optical methods, similar to many of the processes used in semiconductor wafer and chip fabrication (see page 17, line 38 to

page 18, line 2). Other examples include x-ray and electron beam lithography, where the beams can be focused on a particular region of a substrate (see page 29, lines 28 to 35). Protecting groups comprising a sulfonyl moiety are particularly appropriate for electron beam lithography.

Alternatively, deprotection by chemical or some electrical methods can be achieved by the surface topography of a substrate. The specification at page 26, lines 1-5, teaches that the substrate and its surface preferably form a rigid support on which to carry out reactions, and such reactions can take place on raised or depressed regions of the substrate. Item 8 of the glossary (see page 5 of the instant amendment) teaches that it may be desirable to physically separate synthesis regions for different polymers. The specification at page 26, lines 18-26, further teaches that the surface of the substrate can be physically divided, or etched, using well known techniques to provide surface features such as trenches, v-grooves, and mesa structures. One skilled in the art would recognize that trenches in a surface allow one to selectively flow a protecting agent or a deprotecting agent (including electrolyte solutions and electric current) into a selected region of a substrate, thereby selectively activating said trenches.

Applicants' specification discloses several methods of selectively protecting and deprotecting peptides bound to a particular region of a substrate. Applicants have further demonstrated that activating agents other than light were well-known in the art at the time of the instant application's effective filing date. Therefore, Applicants' specification provides sufficient written description of the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 172-184, 186, and 188-192 under 35 U.S.C. § 112, First Paragraph (Enablement)

A. Summary of the Rejection

The Examiner states that the specification is enabling for photolithographic methods in protection and deprotection steps of the present method. However, the Examiner believes that the specification does not provide enablement for the use of other techniques such as chemical or magnetic methods. The Examiner specifically states that there is insufficient enabling disclosure for the use of chemical, thermal, or magnetic techniques to remove the protecting groups from the compounds, so that an activated region on the substrate surface is formed. Also, the

Examiner states that the prior art at the time the invention was made was such that synthesis of an array of compounds on a substrate by selectively protecting and deprotecting using chemical or magnetic methods was difficult or unknown. The Examiner reasons that selectively protecting or deprotecting compounds using chemical or thermal methods is not possible without using other methods such as masking using barriers.

B. Argument

As discussed above, examples of the use of chemical, thermal, and magnetic methods in protecting and deprotecting compounds as part of synthesizing a *single* polypeptide species (i.e., *not* a selective synthesis) on a solid support were known at the time of the invention was made. As the Examiner has acknowledged, Applicants have disclosed how to *selectively* protect and deprotect regions of a substrate using photolithographic methods. The specification additionally teaches chemical, thermal, and electrical methods of *selectively* deprotecting regions of a substrate, which are largely analogous to the photolithographic methods.

In one example, the masks taught in the photolithographic methods are analogous to a solvent-tight barrier (e.g., for chemical and electrochemical methods). An example of an appropriate solvent-tight barrier can be found in U.S. 5,547,839 (hereinafter "Exhibit B"), which is incorporated by reference on page 1, line 31 of the specification. Figure 11 of Exhibit B shows a schematic diagram of a reactor chamber formed by a substrate being sealed to an apparatus comprising entry and exit points for reagents. One skilled in the art would recognize the use of a reaction chamber having a smaller surface area than the substrate, such that one could position the chamber to selectively activate regions of the substrate.

In another example, several of the disclosed deprotection methods use a beam that can be focused onto a specific region of a substrate, thereby deprotecting a selected area and eliminating the need for a mask. Such deprotection methods include x-ray and electron beam lithography (see page 29, lines 28 to 35) and laser methods for thermal deprotection (see page 133, lines 26-38).

In yet another example, selective deprotection of a region of the substrate by chemical or some electrical methods is achieved by the surface topography of a substrate. The specification at page 26, lines 3-5, teaches that the substrate and its surface preferably form a rigid support on

which to carry out reactions. Item 8 of the glossary (see page 5 of the instant amendment) teaches that it may be desirable to physically separate synthesis regions, such as by using wells, raised regions, or etched trenches. The specification at page 26, lines 18-26, further teaches that the surface of the substrate can be physically separated, or etched, using well known techniques to provide surface features such as trenches, v-grooves, and mesa structures. One skilled in the art would recognize that trenches in a surface allow one to selectively flow a protecting agent or a deprotecting agent (including electrolyte solutions and electric current) into a discrete, selected region of a substrate.

Given the teachings of the instant application regarding selectively activating a region of a substrate, a person skilled in the art would be able to prepare a peptide array using activators other than light. Therefore, one skilled in the art would be able to practice the claimed invention without undue experimentation. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By _____

Jesse A. Becker
Registration No.: 52,883
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

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